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In the Written Opinion of March 17, 2004, the novelty and inventive step of the present invention as defined by claims 1 to 11 was questioned. An amended set of 12 claims is submitted. In order to alleviate the prosecution, a further set of claims is submitted, wherein the amendments are introduced in handwritten form into the claims as originally filed.

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Extension - 214

**Via facsimile and
confirmation copy**

Supports for the amendments are found in the description as originally filed as follows:

Claim 1:

"purified or": page 22, lines 21, 26; page 31, line 26; page 32, lines 1 to 3.

"*Moraxella catarrhalis*": claim 2 as originally filed.

"bacteria from": page 1, line 3 and page 18, line 17.

Claim 3:

Is derived from claim 1 as originally filed.

"purified or": page 22, lines 21, 26; page 31, line 26, page 32, lines 1 to 3.

"*Neisseria lactamica*": claim 2 as originally filed.

"bacteria from": page 1, line 3 and page 18, line 17.

"wherein the cross-reactive antigens to *Neisseria meningitidis*

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are oligosaccharides of LOS": Page 19, line 1; page 33, lines 19 to 25.

"which are cross-reactive to human blood group antigens": page 53, lines 23 to 26.

The option "serogroup A" was cancelled from claim 3.

The last line concerning the antibodies was adapted to the amended definition of the antigen.

The following claims were renumbered.

Claim 12 was adapted to the amended claims 1 and 3.

Novelty:

The subject of D1 (Yin-Duo et al.) is the induction of an immune response to *N. meningitidis* serogroup A with purified LOS from *N. lactamica*. The subject of claim 1 is novel over D1, since it concerns a medicament derived from *M. catarrhalis*. Furthermore, the subject of claim 3 is novel, since it teaches the preparation of a medicament comprising a specifically selected antigen. The antigen is an oligosaccharide portion of LOS, which is cross-reactive with *N. meningitidis* of serogroup B, C, H, I, K, L, X, Y, Z, 29E or W135, or non-capsulated meningococcal strains, and furthermore, cross-reactive to human blood group antigens. D1 only discloses cross-reactivity with *N. meningitidis* serogroup A, and does not disclose cross-reactivity with human blood group antigens.

Claim 1 is novel in view of Reference D2, because the subject of D2 are vaccines derived from *N. lactamica* and not from *M. catarrhalis*. The subject of claim 3 is also novel in view of D2. D2 does not disclose or suggest a medicament comprising an antigen of *N. lactamica*, which is the oligosaccharide portion of LOS, with cross-reactivity to antigens of *N. meningitidis* as well as human blood group antigens. In contrary, D2 only provides a general teaching that a vaccine against *N. meningitidis* may be obtained by extracts of *Neisseria*. In the working examples 1, 2 and 3, the *N. lactamica* strain Y92-1009 is used for obtaining purified LOS and fractions comprising LOS, which are whole cells (example 1) and outer membrane preparations (example 2). The strain Y92-1009 was not selected such that the endotoxin oligosaccharide moiety is cross-reactive with antigens to *N. meningitidis* and human blood group antigens. This is clearly demonstrated in example 4, which shows that

all mice vaccinated with LOS, purified according to example 3, died within a few days. It can clearly be deduced that the immunization effect obtained with preparations according to example 1 and 2 is not due to the endotoxin, let alone the oligosaccharide portions of the endotoxin. The immunization effect must, in contrary, result from the membrane protein. Therefore, the preparation according to example 3 is different from a medicament according to claim 1 of the present invention.

The subject of D3 are conjugates, which elicit a cross-reactive immune response triggered by the conserved portions of the lipopolysaccharides of gram negative bacteria. In section [0016] there is a list of bacteria given, which are potentially suited for such a treatment, amongst which are *N. meningitidis* and *M. catarrhalis*. Nonetheless, D3 does not disclose to elicit a cross-reactive antibody response with extracts of *M. catarrhalis* in the treatment of *N. meningitidis*, because both bacteria do not share a common core structure or the same lipid A moieties, as required by D3.

The structure of LOS from *N. meningitidis* and *M. catarrhalis* is shown in the present application in the figure on page 15 of the description. Lipid A of *N. meningitidis* comprises one single strand fatty acid with 12 carbon molecules, and a second with a 14C branched with a 12C strand. *M. catarrhalis* contains a structurally different lipid A with one molecule showing a single C12, and a branched c12: c10 strand, while the second lipid A molecules comprise one c12: c10 and one c12: c12 branched strand. The only structural homology of LOS cause structure between the two species is found in the two KDO molecules attached to lipid A. In the *N. meningitidis* LPS, a heptose molecule is attached to the first KDO as the base of the inner cause structure, whereas in *M. catarrhalis* LOS a glucose is attached. The second heptose molecule from *N. meningitidis* is absent in *M. catarrhalis* LOS. Considering those differences, it is clear that D3 does not disclose or suggest a medicament according to claim 1 of the present invention. In D3, *M. catarrhalis* is only mentioned specifically in section [0037], where a surface protein of *M. catarrhalis* is named as a useful carrier protein.

With respect to the distinction of the subject of the invention over D3 and the other references, the attention of the Examining Authority is also kindly directed to page

12, line 29 to page 16, line 2 in the description, wherein the state of the art of D1 to D3 is acknowledged.

In summary, the subject of the invention as defined by claims 1 to 12 is novel over the state of the art.

Inventive step:

Concerning the assessment of inventive step, the Examining Authority's attention is also kindly directed to the passage from page 12 to page 16, wherein the state of the art is acknowledged.

The invention is made in the field of vaccination and treatment of *N. meningitidis*. The closest prior art is thus either document D1 or D2. Both documents are related to the treatment or vaccination against *N. meningitidis* with endotoxin of the commensal *N. lactamica*. It is likely that the inventors of D1 and D2 realized that the endotoxins of *N. lactamica* are of low toxicity.

Nonetheless, the problem remains that many medicaments obtained that way are non-functional. The problems of the state of the art in general are discussed in detail in the description from pages 1 to 11. The problem is to provide vaccines which are highly immunogenic, have a long-lasting effect and are effective in children and adults. A specific problem is to provide a vaccine against serogroup B which is not yet available. A problem of the state of the art, and especially of D1 and D2 is that the vaccines are often not functional, which will often result in the death of the patient.

The solution according to the present invention is to specifically select the glycoconjugates and/or lipooligosaccharides, such that it is derived from *M. catarrhalis* with cross-reactive antigens to *N. meningitidis*. A further solution of the invention is a medicament comprising glycoconjugates or lipooligosaccharides from *N. lactamica* with cross-reactive antigens to *N. meningitidis*, wherein the antigens are oligosaccharides of LOS, which are cross-reactive to human blood group antigens. In both solutions, alternatively antibodies may be applied.

The solution according to the present invention was neither disclosed nor suggested from the state of the art of D1 to D3. The references share the same scientific knowledge background. According to the state of the art, commensal LOS were considered to be potential vaccines due to their lipid A and core moieties. In contrary, the oligosaccharide moieties were considered as not relevant for vaccination processes, because the oligosaccharide chain of *N. meningitidis* shows a high variation.

The subject of D1 - D3 is the induction of **bactericidal** antibodies to endotoxins from meningococci by the lipid A and core portions of *N. lactamica* (see abstract of D1, line 1) LOS. There is no teaching or suggestion how other functional antibodies, particularly cross-reactive antibodies to lipooligosaccharides with anti-inflammatory and/or opsono-phagocytic activity, as obtained by the present application, might be obtained.

These differences in the functionality of antibodies are crucial, and were a surprising discovery of the inventors developing both anti-meningococcal vaccines, and therapeutic antibodies against meningococcal disease.

When immunizing animals (i.e. mice) with outer membrane vesicles, isolated LOS, or whole *N. meningitidis* or *N. lactamica* according to D1 to D3, these animals develop a strong titer of bactericidal antibodies against the endotoxin carbohydrate moieties, particularly the human blood group like structures paragloboside, and the Ii antigens, while induce none or little immunotoxicity.

The inventors showed that this effective bactericidal immune response is only possible, because mice (or other rodent species) do not carry these human blood group antigens, and are, therefore, able to recognize these antigens as foreign. Similar results were found when immunizing mice with the polysaccharide capsule of group B meningococci, that is identical with the human self antigen ICAM, a neural carbohydrate. These mice developed a strong bactericidal antibody titer against ICAM.

Nonetheless, the results obtained in the mouse model of D1 or D2 are **not transferable to humans**. When challenging humans with either human blood group antigens, or ICAM, no or little immunoprotection with bactericidal antibodies could be induced, and most of the vaccine candidates were found to be immunotoxic.

The inventors of the present invention have developed a mouse model mimicking the blood group phenotype found in humans by inducing immunotolerance against these antigens. These animals do not detect the human blood group antigens as a foreign molecule, because their immune system considers the blood group molecules as self antigens, a phenotype that has not been available before. When immunizing these novel mice with defined meningococcal or commensal carbohydrate antigens (i.e. LOS), no significant titers of bactericidal antibodies against the human blood group moieties were induced, similarly as seen in humans. But surprisingly, instead of bactericidal antibodies, high titers of antibodies specific for the blood group moieties with anti-inflammatory potency were found.

Following this new understanding of the induction of functional immunity against self antigens, mice from this new mouse model were challenged with isolated blood group antigens obtained from bacteria, as well as non-conjugated antigens obtained from human cells (i.e. (sialyl-) paragloboside, li, pK, and/or P antigens) from human blood or tissue, or conjugated antigens to a toxoid were used (tables 1 and 2). Again, no significant titers of bactericidal antibodies against the human blood group antigens were found, but effective functional anti-inflammatory, opsonising and/or phagocytic antibodies were induced. These findings show for the first time that an immunization schedule using self antigens can induce significant amounts of biological functional antibodies recognizing epitopes found on these self antigens. In other experiments the inventors could show that these antigens could induce protective immunity from infection with meningococci, and that these antibodies could be used as passive vaccines during experimental meningitis and sepsis in mice.

These surprising findings show for the first time that the use of vaccines containing human blood group antigens induce biological functional and protective immunity against self antigens with antibodies that elicit anti-inflammatory, opsonic and/or phagocytic immunoprotection.

Therefore, a medicament according to claim 1 or claim 3 of the application is inventive in view of state of the art. According to the state of the art, there was no suggestion to use commensal *M. catarrhalis* in order to prepare a medicament according

to claim 1. Furthermore, there was no suggestion to use *N. lactamica* with cross-reactive antigens to *N. meningitidis*, which are oligosaccharides of LOS, and which are cross-reactive to human blood group antigens. The medicament according to claim 1 provides an alternative to medicaments of the state of the art. If the mouse model results of D1 or D2 would be transferred to humans, the treatment would frequently lead to immunotoxicity and a lethal outcome. The inventive medicaments of claims 2 and 3 surprisingly avoid such effects. The subject of the invention is inventive in view of the state of the art.

Since the subject of claims 1 to 3 is novel and inventive, the subject of the dependent claims 4 to 12 is novel and inventive as well.

It is kindly requested to acknowledge the patentability of the present invention.

Dr. Meyers


The Patent Attorney

Enclosures: /2